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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
11/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/441,055	USUDA ET AL.	
	Examiner	Art Unit	
	CHRISTIAN L. FRONDA	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35 and 41-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35,41-43,45,46,48,51,58 and 59* is/are rejected.

7)☒ Claim(s) *44,47,49,50 and 52-55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/5/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the previous Office Action dated 02/07/2008 has been withdrawn. The rejection of the claims under 35 U.S.C. 103(a) has been withdrawn in view of applicants' arguments filed 08/21/2008. New rejection and new grounds of rejection are presented in the instant Office Action.

2. Claims 31, 35, and 41-59 are pending and under consideration in this Office Action.

3. References AO and AP cited in the PTO form 1449 of the IDS filed 05/05/2008 have not been considered because English translations of these Japanese patents have not been provided.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 56 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recited the phrase "replacement of the amino acid residue Arg-378 and subsequent amino acid residues" which renders the claims vague and indefinite. The metes and bounds of the claims are not certain since it is unclear as to what specific "subsequent amino acid residues" are to be modified.

Claim Rejections - 35 U.S.C. § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

According to MPEP 2143:

> "Exemplary rationales that may support a conclusion of obviousness include:
>
> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) " Obvious to try " – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.
>
> Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel."

7. Claims 31, 35, 41-43, 45, 46, 48, 51, 58, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michaeli et al. (Advances in Polyamine Research (1983), 4, 519-20;

PTO 892) in view of the combined teachings of Parsot et al. (Mol Microbiol. 1987 Jul;1(1):45-52; PTO 892), Malumbres et al. (Appl Environ Microbiol. 1994 Jul;60(7):2209-19; PTO 892), Greene (Escherichia coli and Salmonella Cellular and Molecular Biology, 2nd Edition, pps. 542-560, "BIOSYNTHESIS OF METHIONINE", 1996; PTO 1449 of IDS dated 02/16/2000), and Park et al. (Bioorg Med Chem. 1996 Dec;4(12):2179-85; reference of record).

Michaeli et al. teach a process for producing L-methionine comprising culturing in culture media recombinant *E.coli* host cells having multicopy plasmids containing the *metA* gene which codes for homoserine transsuccinylase, the first enzyme in the methionine biosynthesis pathway, where these recombinant *E.coli* host cells having multicopy plasmids containing the *metA* gene are overproduces of L-methionine. See entire publication especially Table 1 on page 520.

The claims differ from the teachings of Michaeli et al. in that Michaeli et al. does not teach that the recombinant *E.coli* exhibits L-threonine auxotrophy, is deficient in the *metJ* gene encoding a repressor of the L-methionine biosynthesis system, the activity of the S-adenosylmethionine synthetase encoded by the endogenous *metK* gene is reduced, and has enhanced activity of intracellular cystathionine γ-synthase encoded by the *metB* gene and aspartokinase-homoserine dehydrogenase encoded by the *metL* gene.

Parsot et al. teach an *E.coli* threonine auxotroph having a *thrB* mutation, and that the threonine biosynthetic pathway in *E.coli* is composed of aspartokinase l-homoserine dehydrogenase I encoded by the *thrA* gene, homoserine kinase encoded by the *thrB* gene, and threonine synthase encoded by the *thrC* gene. See entire publication especially pages 45-50.

Malumbres et al. teach *E.coli thrA, thrB*, and *thrC* auxotrophs. Malumbres et al. teach that the *E.coli* threonine operon is composed of *thrA* gene encoding aspartokinase l-homoserine dehydrogenase I, *thrB* encoding homoserine kinase, and *thrC* encoding threonine synthase. See entire publication especially pages 2209-2213 and Table 1.

Greene teaches the *E.coli* repressor of the L-methionine biosynthesis system encoded by the *metJ* gene, the *E.coli* methionine biosynthetic enzymes of homoserine transsuccinylase encoded by the *metA* gene, cystathionine γ-synthase encoded by the *metB* gene, and aspartokinase-homoserine dehydrogenase encoded by the *metL* gene. See entire publication, especially pages 542- 553 and Figure 1.

Park et al. teach the enzyme *E.coli metk* gene encoding S-adenosylmethionine synthetase which catalyzes the synthesis of S-adenosyl-L-methionine (SAM), where SAM is a major methyl group transfer agent in biological systems and the methyl moiety of SAM is transferred to proteins, lipids, nucleic acids, and vitamins by SAM-dependent methyltransferases. See abstract and entire publication.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the *E.coli* threonine auxotroph of Parsot et al. such that the *thrC* gene is inactivated by deletion as taught by Malumbres et al.; the *metJ* gene encoding the *E.coli* L-methionine biosynthesis repressor is inactivated and the *E.coli* L-methionine biosynthetic genes of *metA, metB,* and *metL* encoding homoserine transsuccinylase, cystathionine γ-synthase, aspartokinase-homoserine dehydrogenase, respectively, are overexpressed as taught by Green by increasing copy number or replacing their respective native promoter with a stronger promoter; and the *E.coli metk* gene encoding the S-adenosylmethionine synthetase is inactivated. It would have been obvious to one of ordinary skill in the art to then modify the method of Michaeli et al. by substituting the *E.coli* host cell of Michaeli et al. with the modified *E.coli* threonine auxotroph of Parsot et al. as stated above and collecting the produced L-methionine from the culture medium. One of ordinary skill in the art at the time the invention was made would have been motivated to do this for the purposes of having a simple culturing method that produces large amount of L-methionine from culturing the modified *E.coli* threonine auxotroph of Parsot et al. as stated above.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since recombinant molecular biology techniques for inactivating genes and overexpressing genes in *E.coli* are well known and developed in the art.

One of ordinary skill in the art at the time the invention was made would predict and have the expectation that the modified *E.coli* threonine auxotroph of Parsot et al. as stated above would produce large amounts of L-methionine by inactivating the *metJ* gene encoding the repressor of methionine biosynthesis and overexpressing the L-methionine biosynthetic genes of *metA, metB,* and *metL* encoding homoserine transsuccinylase, cystathionine γ-synthase, aspartokinase-homoserine dehydrogenase, respectively, since Michaeli et al. teach that *E.coli* overexpressing the L-methionine biosynthetic *metA* gene are overproducers of L-methionine and inactivating the repressor of the L-methionine biosynthesis encoded by *metJ* would allow for derepressed biosynthesis of L-methionine. One of ordinary skill in the art at the time the invention was made would predict and have the expectation that the modified *E.coli* threonine auxotroph of Parsot et al. as stated above would produce large amounts of L-methionine because inactivating the *thrC* gene encoding the threonine synthase is expected to reduce or prevent the produced L-methionine from being converted or metabolized to threonine. One of ordinary skill in the art at the time the invention was made would predict and have the expectation that the modified *E.coli* threonine auxotroph of Parsot et al. as stated above would produce large amounts of L-methionine because inactivating *metk* gene encoding S-adenosylmethionine synthetase is expected to reduce or prevent the produced L-methionine from being converted or metabolized to S-adenosyl-L-methionine.

Conclusion

8. No claim is allowed.

9. Claims 44, 47, 49, 50, and 52-55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM - 6:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571)272-0934. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian L. Fronda/
Primary Examiner
Art Unit 1652